Agenda

- Robert A. Fromtling, PhD
  - Introduction

- Bach-Yen Nguyen, MD
  - Raltegravir Background
  - Clinical Development Program Overview
  - Clinical Trials Results
    - Efficacy
    - Resistance
    - Safety

- Robin Isaacs, MD
  - Drug-Drug Interactions
  - Risk Management Plan
  - Conclusions
Current Antiretroviral Armamentarium

- Fusion inhibitors
- Mature virus
- Reverse transcriptase inhibitors
- Integrase inhibitors
- Protease inhibitors

Adapted from clinicaloptions.com/hiv.
Approved antiretroviral therapies belong to 4 classes:
Current Antiretroviral Armamentarium

- Fusion inhibitors
- Mature virus
- Integrase inhibitors
- Protease inhibitors
- Reverse transcriptase inhibitors

Approved antiretroviral therapies belong to 4 classes:
  - Nucleoside reverse transcriptase inhibitors (NRTIs)
  - Non-nucleoside reverse transcriptase inhibitors (NNRTIs)
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- Nucleoside reverse transcriptase inhibitors (NRTIs)
- Non-nucleoside reverse transcriptase inhibitors (NNRTIs)
- Protease inhibitors (PIs)
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- Nucleoside reverse transcriptase inhibitors (NRTIs)
- Non-nucleoside reverse transcriptase inhibitors (NNRTIs)
- Protease inhibitors (PIs)
- Fusion inhibitors
Current Antiretroviral Armamentarium

Approved antiretroviral therapies belong to 4 classes:
- Nucleoside reverse transcriptase inhibitors (NRTIs)
- Non-nucleoside reverse transcriptase inhibitors (NNRTIs)
- Protease inhibitors (PIs)
- Fusion inhibitors

HIV integrase enzyme represents a novel target for therapy
- It catalyzes the integration of viral DNA into host cellular DNA, a critical step for viral replication
Inhibition of Integrase Strand Transfer Shifts the Fate of HIV-1 DNA Resulting in an Irreversible Block to Infection

Integrase binds to the viral DNA and catalytically processes 3’ ends (3’ end processing)

Preintegration complex

LTRs = long terminal repeats.
Inhibition of Integrase Strand Transfer Shifts the Fate of HIV-1 DNA Resulting in an Irreversible Block to Infection

Integrase binds to the viral DNA and catalytically processes 3’ ends (3’ end processing)

Preintegration complex

Integrase joins viral and cellular DNA (Strand transfer)

Integration

*Gap repair/ligation

LTRs = long terminal repeats. * Cellular functions.
Integrase binds to the viral DNA and catalytically processes 3’ ends (3’ end processing)

Preintegration complex

Integrase joins viral and cellular DNA (Strand transfer)

Integration

*Gap repair/ligation

Raltegravir blocks strand transfer

Degradation or recombination and repair*

1 and 2 LTR circles

LTRs = long terminal repeats. * Cellular functions.
In vitro Activity

- Potent in vitro activity
  - $IC_{95} (\text{Mean} \pm \text{SD}) = 31 \text{ nM} \pm 20 \text{ nM}$ in 50% NHS
  - Active against:
    - Multi-drug resistant HIV-1
    - CCR5 and CXCR4 HIV-1
  - HIV-1 resistant to raltegravir remain sensitive to other antiretroviral classes
  - Additive/synergistic in vitro with NRTIs, NNRTIs, PIs, and enfuvirtide

- Raltegravir is not genotoxic in in vitro and in vivo assays
Pharmacokinetics

- Raltegravir pharmacokinetics support BID dosing
  - Terminal \( t_{1/2} \) ~9 hours with a shorter \( \alpha \)-phase \( t_{1/2} \) ~1 hour
  - Slight degree of accumulation in \( C_{12hr} \) with multiple doses

- Considerable variability was observed in the clinical pharmacokinetics of raltegravir
  - For observed \( C_{12hr} \) in Phase III
    - CV for inter-subject variability = 212%
    - CV for intra-subject variability = 122%

- In Phase I studies, doses as high as 800 mg p.o. BID were generally well tolerated
  - At 100 mg BID, mean \( C_{12hr} > IC_{95} \)
  - Pharmacokinetics similar across
    - Gender, race, age (adults), HIV infection status, hepatic function, renal function, and body mass index
Absorption, Metabolism, and Excretion

- Rapidly absorbed: $T_{\text{max}} \sim 3$ hours

- Food effect
  - Phase II and III studies were conducted with dosing without regard to food
  - Exposure similar in fed (high-fat meal) and fasted states
  - A high-fat meal appeared to slow rate and extend duration of absorption
    - 7.4 hour delay in $T_{\text{max}}$
    - 34% decrease in $C_{\text{max}}$
    - 8.5-fold increase in $C_{\text{12 hr}}$

- Metabolism and excretion
  - Major mechanism of clearance is glucuronidation
    - Mediated by UGT1A1
  - Renal elimination is minor
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Clinical Development Program

Phase I
18 studies
Total N=315
Clinical Development Program

Phase I
18 studies
Total N=315

Dose-Finding
P004

Phase Ib
Monotherapy
N=35

Phase II
Treatment-
Naïve
N=201
Clinical Development Program

Phase I
18 studies
Total N=315

Dose-Finding P005
Phase II
Treatment-Experienced
N=179

Dose-Finding P004
Phase Ib
Monotherapy
N=35

Phase II
Treatment-Naïve
N=201
Clinical Development Program

Phase I
18 studies
Total N=315

Dose-Finding P005
Phase II
Treatment-Experienced
N=179

P018 & P019
Phase III
(2 studies)
Treatment-Experienced
Total N=703

NDA
April 2007

Dose-Finding P004

Phase Ib
Monotherapy
N=35

Phase II
Treatment-Naïve
N=201
Clinical Development Program

ADDITIONAL ONGOING STUDIES

Worldwide Expanded Access (N>5,000)

- Phase III Treatment-Naïve (N=550)
- Phase III (2 studies) Switch From Kaletra™ to Raltegravir (N=680)
- Pediatric Study (N~120)

Phase I
18 studies Total N=315

Dose-Finding P005
Phase II Treatment-Experienced N=179

P018 & P019
Phase III (2 studies) Treatment-Experienced Total N=703

NDA April 2007

Dose-Finding P004

- Phase Ib Monotherapy N=35
  - Phase II Treatment-Naïve N=201
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Phase II Dose Finding Studies

- **Treatment-naïve (Protocol 004)**
  - Doses: 100, 200, 400, and 600 mg BID†
  - Comparator: Efavirenz
  - Regimen: In combination with tenofovir and lamivudine

- **Treatment-experienced (Protocol 005)**
  - Doses: 200, 400, and 600 mg BID†
  - Comparator: Placebo
  - Regimen: In combination with optimized background therapy (OBT)
  No investigational drugs allowed in OBT

† Twice daily dosing approximately 10-14 hours apart.
Phase II Treatment-Experienced (Protocol 005) Percent of Patients (95% CI) With <400 copies/mL

**Percent of Patients (95% CI) With <400 copies/mL†**

* Plus OBT.
† Non-completer = failure approach.

**Percent of Patients With HIV RNA <400 copies/mL**

- **Double-Blind Only**
  - Placebo*
    - Number of contributing patients: 43
  - Raltegravir 200 mg BID*
    - Number of contributing patients: 43
  - Raltegravir 400 mg BID*
    - Number of contributing patients: 45
  - Raltegravir 600 mg BID*
    - Number of contributing patients: 45

- **Double-Blind Plus Open Label**
  - Placebo*
    - Number of contributing patients: 45
  - Raltegravir 200 mg BID*
    - Number of contributing patients: 42
  - Raltegravir 400 mg BID*
    - Number of contributing patients: 44
  - Raltegravir 600 mg BID*
    - Number of contributing patients: 45

* Plus OBT.
† Non-completer = failure approach.
Selection of Phase III Dosing Regimen

- Results of Phase II dose-ranging studies
  - No differentiation of doses based on efficacy or safety through 48-week
    - All doses studied demonstrated potent and sustained efficacy
    - No dose-limiting or dose-related toxicities
  - Extensive pharmacokinetic/pharmacodynamic analyses did not identify a relationship between raltegravir pharmacokinetics and treatment outcomes
    - Raltegravir doses studied in combination regimens likely on plateau of dose-response curve

400 mg BID selected as Phase III dose

Provides a margin for safety and efficacy when raltegravir is co-administered with drugs that are inhibitors or inducers of UGT1A1
Phase III Study Design (1)

- Randomized, double-blind, placebo-controlled with Data and Safety Monitoring Board
- Primary analysis at Week 16

**Primary endpoints:**

- Week 16

**Planned duration:**

- Week 156

**Drug Allocation:**

- Raltegravir 400 mg BID + OBT
  - Protocol 018 (n=234)
  - Protocol 019 (n=232)

- Placebo + OBT
  - Protocol 018 (n=118)
  - Protocol 019 (n=119)

**Inclusion Criteria:**

- HIV-1-infected
- Triple-class resistant
- HIV-1 RNA >1000 copies/mL
- No CD4 cell cut-off
- Protocol 018 (N=352) (Europe, Asia/Pacific and Peru)
- Protocol 019 (N=351) (North and South America)

- Selected investigational antiretrovirals, darunavir and tipranavir, permitted in OBT
Phase III Study Design (2)

- **Primary Efficacy Endpoint**
  - Percent of patients with HIV-1 RNA <400 copies/mL at Week 16

- **Key Secondary Endpoints**
  - Percent of patients with HIV-1 RNA <50 copies/mL at Week 16
  - Change from baseline in CD4 cell count at Week 16

- Patients with virologic failure after ≥16 weeks of therapy could enter an open-label post-virologic failure (OLPVF) raltegravir arm
Key Definitions

- Definition of virologic failure
  - Non-responder
    - $< 1 \log_{10} \downarrow$ HIV RNA from baseline and HIV RNA $>400$ copies/mL at Week 16
  - Relapse
    - $> 1 \log_{10} \uparrow$ HIV RNA above nadir
    - OR
      - $>400$ copies/mL after initial response $<400$ copies/mL

- Genotypic (GSS) and phenotypic (PSS) sensitivity score
  - “Active” drug in the OBT defined by results of PhenosenseGT™ (Monogram Biosciences) testing at baseline
  - For each “active” drug in OBT, +1 added to score
  - For enfuvirtide
    - +1 added to score for use in enfuvirtide-naïve patients
  - For darunavir
    - +1 added to score for use in darunavir-naïve patients
# Patient Disposition

<table>
<thead>
<tr>
<th></th>
<th>Protocol 018</th>
<th>Protocol 019</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screened</td>
<td>500</td>
<td>512</td>
</tr>
<tr>
<td>Randomized</td>
<td>352</td>
<td>351</td>
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</table>
## Patient Disposition

<table>
<thead>
<tr>
<th></th>
<th>Protocol 018</th>
<th></th>
<th>Protocol 019</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Screened</td>
<td>500</td>
<td></td>
<td>512</td>
<td></td>
</tr>
<tr>
<td>Randomized</td>
<td>↓</td>
<td>352</td>
<td>↓</td>
<td>351</td>
</tr>
<tr>
<td>Randomized</td>
<td></td>
<td>Raltegravir†</td>
<td>234</td>
<td>Raltegravir†</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Placebo†</td>
<td>118</td>
<td>Placebo†</td>
</tr>
<tr>
<td>Treated</td>
<td>232</td>
<td></td>
<td>230</td>
<td></td>
</tr>
<tr>
<td></td>
<td>↓</td>
<td></td>
<td>↓</td>
<td></td>
</tr>
<tr>
<td>Continuing on</td>
<td>212</td>
<td></td>
<td>201</td>
<td></td>
</tr>
<tr>
<td>double-blind</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>therapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

† Plus OBT.
## Patient Disposition

| Protocol 018 | | Protocol 019 | |
|-------------|-------------|-------------|
| **Screened** | 500 | 512 |
| **Randomized** | 352 | 351 |
| **Randomized** | Raltegravir† | Placebo† | Raltegravir† | Placebo† |
| | 234 | 118 | 232 | 119 |
| **Treated** | 232 | 118 | 230 | 119 |
| **Continuing on double-blind therapy** | 212 | 68 | 201 | 77 |
| **Discontinued therapy** | 20 | 50 | 29 | 42 |
| **Entered OLPVF** | 15 | 46 | 19 | 39 |
| **Discontinued due to AE** | 4 | 4 | 5 | 1 |
| **Discontinued due to other** | 1 | 0 | 5 | 2 |

† Plus OBT; OLPVF = open-label post-virologic failure arm; AE = adverse experience.
## Baseline Patient Characteristics

<table>
<thead>
<tr>
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<th>Protocol 018</th>
<th></th>
<th>Protocol 019</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Raltegravir†</td>
<td>Placebo†</td>
<td>Raltegravir†</td>
<td>Placebo†</td>
</tr>
<tr>
<td></td>
<td>N=232</td>
<td>N=118</td>
<td>N=230</td>
<td>N=119</td>
</tr>
<tr>
<td>Median age, years</td>
<td>46</td>
<td>43</td>
<td>45</td>
<td>46</td>
</tr>
<tr>
<td>Male (%)</td>
<td>84</td>
<td>87</td>
<td>91</td>
<td>90</td>
</tr>
<tr>
<td>Caucasian (%)</td>
<td>75</td>
<td>81</td>
<td>55</td>
<td>65</td>
</tr>
<tr>
<td>Median CD4 count,</td>
<td>140</td>
<td>105</td>
<td>102</td>
<td>132</td>
</tr>
<tr>
<td>cells/mm³</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GM viral load, copies/mL (log₁₀ HIV RNA)</td>
<td>40,519 (4.6)</td>
<td>31,828 (4.5)</td>
<td>48,366 (4.7)</td>
<td>47,789 (4.7)</td>
</tr>
<tr>
<td>AIDS (%)</td>
<td>94</td>
<td>90</td>
<td>91</td>
<td>92</td>
</tr>
<tr>
<td>Median years of prior ARTs (median # ART)</td>
<td>11 (12)</td>
<td>10 (12)</td>
<td>10 (12)</td>
<td>10 (12)</td>
</tr>
<tr>
<td>Hepatitis status</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatitis B (%)</td>
<td>8</td>
<td>4</td>
<td>10</td>
<td>3</td>
</tr>
<tr>
<td>Hepatitis C (%)</td>
<td>15</td>
<td>20</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

† Plus OBT; GM = geometric mean; ART = antiretroviral therapy.
## Characteristics of Optimized Background Therapy

<table>
<thead>
<tr>
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<th>Protocol 018</th>
<th></th>
<th>Protocol 019</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Raltegravir †</td>
<td>Placebo †</td>
<td>Raltegravir †</td>
<td>Placebo †</td>
</tr>
<tr>
<td></td>
<td>N=232</td>
<td>N=118</td>
<td>N=230</td>
<td>N=119</td>
</tr>
<tr>
<td></td>
<td>%</td>
<td>%</td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>GSS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GSS = 0</td>
<td>30</td>
<td>29</td>
<td>20</td>
<td>26</td>
</tr>
<tr>
<td>GSS = 1</td>
<td>33</td>
<td>41</td>
<td>44</td>
<td>40</td>
</tr>
<tr>
<td>PSS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PSS = 0</td>
<td>19</td>
<td>18</td>
<td>10</td>
<td>19</td>
</tr>
<tr>
<td>PSS = 1</td>
<td>29</td>
<td>33</td>
<td>34</td>
<td>27</td>
</tr>
<tr>
<td>New enfuvirtide in OBT</td>
<td>21</td>
<td>20</td>
<td>19</td>
<td>20</td>
</tr>
<tr>
<td>New darunavir in OBT</td>
<td>27</td>
<td>25</td>
<td>45</td>
<td>50</td>
</tr>
</tbody>
</table>

† Plus OBT.

GSS = genotypic sensitivity score; PSS = phenotypic sensitivity score; OBT = optimized background therapy.
Phase III Treatment-Experienced (Protocol 018)
Percent of Patients (95% CI) With <400 copies/mL*

<table>
<thead>
<tr>
<th>Weeks</th>
<th>Raltegravir BID + OBT</th>
<th>Placebo + OBT</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>232</td>
<td>118</td>
</tr>
<tr>
<td>2</td>
<td>232</td>
<td>118</td>
</tr>
<tr>
<td>4</td>
<td>231</td>
<td>118</td>
</tr>
<tr>
<td>8</td>
<td>231</td>
<td>118</td>
</tr>
<tr>
<td>12</td>
<td>230</td>
<td>118</td>
</tr>
<tr>
<td>16</td>
<td>230</td>
<td>118</td>
</tr>
<tr>
<td>24</td>
<td>230</td>
<td>118</td>
</tr>
</tbody>
</table>

Percent of Patients With HIV RNA <400 copies/mL

- 77% at 24 weeks
- 75% at 24 weeks

p<0.001

* Non-completer = failure approach.
Phase III Treatment-Experienced (Protocol 019) Percent of Patients (95% CI) With <400 copies/mL*

*p<0.001

Percent of Patients With HIV RNA <400 copies/mL

Number of Contributing Patients

Raltegravir BID + OBT: 230 230 228 227 230 229 128
Placebo + OBT: 119 119 119 118 119 119 69

* Non-completer = failure approach.
Phase III Treatment-Experienced Protocol 018 and Protocol 019 Integrated Analysis of Efficacy
Treatment-Experienced Patients
Integrated Analysis of Efficacy

Percent of Patients With HIV RNA <400 copies/mL

Percent of Patients With HIV RNA <50 copies/mL

Change From Baseline in CD4 Cell Count

For HIV RNA <400 copies/mL and <50 copies/mL: Non-completer = failure approach.
For CD4: Baseline carried forward for virologic failures.
### Protocols 018 and 019 Combined Efficacy†
#### Percent of Patients With HIV RNA <400 copies/mL at Week 16 by Baseline HIV RNA and CD4 Cell Count

<table>
<thead>
<tr>
<th>Baseline HIV RNA copies/mL</th>
<th>N</th>
<th>Percent of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;100,000</td>
<td>159</td>
<td>64</td>
</tr>
<tr>
<td></td>
<td>75</td>
<td>19</td>
</tr>
<tr>
<td>≤100,000</td>
<td>288</td>
<td>88</td>
</tr>
<tr>
<td></td>
<td>155</td>
<td>55</td>
</tr>
<tr>
<td>CD4 cells/mm³</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤50</td>
<td>140</td>
<td>63</td>
</tr>
<tr>
<td></td>
<td>75</td>
<td>24</td>
</tr>
<tr>
<td>&gt;50 and ≤200</td>
<td>168</td>
<td>86</td>
</tr>
<tr>
<td></td>
<td>82</td>
<td>46</td>
</tr>
<tr>
<td>&gt;200</td>
<td>138</td>
<td>88</td>
</tr>
<tr>
<td></td>
<td>73</td>
<td>59</td>
</tr>
</tbody>
</table>

† Virological failures carried forward.
Protocols 018 and 019 Combined Efficacy†
Percent of Patients With HIV RNA <400 copies/mL at Week 16 by Genotypic Sensitivity Score (GSS)

<table>
<thead>
<tr>
<th>GSS</th>
<th>N</th>
<th>Percent of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>111</td>
<td>57</td>
</tr>
<tr>
<td></td>
<td>63</td>
<td>10</td>
</tr>
<tr>
<td>1</td>
<td>170</td>
<td>85</td>
</tr>
<tr>
<td></td>
<td>93</td>
<td>43</td>
</tr>
<tr>
<td>2 or more</td>
<td>159</td>
<td>89</td>
</tr>
<tr>
<td></td>
<td>70</td>
<td>71</td>
</tr>
</tbody>
</table>

† Virological failures carried forward.
**Protocols 018 and 019 Combined Efficacy†**

Percent of Patients With HIV RNA <400 copies/mL at Week 16 by First Use of Selected ARTs in OBT

<table>
<thead>
<tr>
<th>Enfuvirtide</th>
<th>Darunavir</th>
<th>N</th>
<th>Percent of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>+</td>
<td>+</td>
<td>44</td>
<td>98</td>
</tr>
<tr>
<td>+</td>
<td>-</td>
<td>23</td>
<td>87</td>
</tr>
<tr>
<td>+</td>
<td>-</td>
<td>42</td>
<td>90</td>
</tr>
<tr>
<td>-</td>
<td>+</td>
<td>80</td>
<td>90</td>
</tr>
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<td>-</td>
<td>-</td>
<td>47</td>
<td>74</td>
</tr>
<tr>
<td>-</td>
<td>-</td>
<td>191</td>
<td>29</td>
</tr>
</tbody>
</table>

+ : First use in OBT  
- : Not used in OBT  
† Virological failures carried forward.
Consistent Treatment Effect Regardless of Gender, Race, Region, and Viral Sub-type

Treatment Difference (Raltegravir - Placebo) (95% CI) at Week 16

HIV RNA <400 copies/mL (%)
Favors PBO Favors RAL

HIV RNA <50 copies/mL (%)
Favors PBO Favors RAL

CD4 Cell Counts (cells/mm³)
Favors PBO Favors RAL

Male (N=615) Favors RAL
Female (N=84) Favors PBO

White (N=474) Favors RAL
Black (N=92) Favors PBO
Hispanic (N=72) Favors PBO

North America (N=291) Favors PBO
South America (N=92) Favors PBO
Asia Pacific (N=58) Favors PBO
Europe (N=258) Favors RAL

Clade B virus (N=632) Favors PBO
Non-Clade B virus (N=56) Favors RAL

RAL = raltegravir; PBO = placebo.
Efficacy Conclusions

- In HIV-1-infected patients failing antiretroviral therapy with triple-class resistant HIV, raltegravir 400 mg BID plus OBT
  - Has rapid, potent, and superior antiretroviral and immunological efficacy compared to placebo plus OBT
    - In patients receiving new, active antiretroviral therapies in OBT, e.g., enfuvirtide and/or darunavir, ≥90% achieved HIV RNA <400 copies /mL
    - The treatment effect of raltegravir is consistent regardless of baseline viral load, CD4 cell count, GSS, PSS, selected ARTs in OBT, gender, race, geographic region, and viral subtype
  - Has sustained efficacy in patients followed to Week 48 in the Phase II study
Agenda

- Robert A. Fromtling, PhD
  - Introduction

- Bach-Yen Nguyen, MD
  - Raltegravir Background
  - Clinical Development Program Overview
  - Clinical Trials Results
    - Efficacy
    - Resistance
    - Safety

- Robin Isaacs, MD
  - Drug-Drug Interactions
  - Risk Management Plan
  - Conclusions
Analysis of Raltegravir Resistance Genotyping Results from Protocols 005, 018, and 019

- In patients with triple-class resistant virus, virologic failure on raltegravir was observed in 38 patients in Protocol 005.

- Genotype data available for all 38 failures in Protocol 005:
  - Most patients (35/38) failing raltegravir had integrase mutations conferring raltegravir resistance.
  - Integrase mutations were in either of two genetic pathways (N155 or Q148) in 34 of 35 patients.
  - Resistance was typically associated with two or more mutations (31 of 35 patients).
    - Q148H/G140S was most common (N=13).
  - No association between dose and/or drug concentration and resistance.

- Partial genotype data available for Protocols 018 and 019 showed similar findings.
Integrase Mutations Associated With Raltegravir Virologic Failure Confer Raltegravir Resistance

Multiple mutations engender higher-level resistance than single mutation.
Raltegravir Resistance and Clinical Implication

- In patients failing a raltegravir-containing regimen, the HIV isolate often displayed integrase mutations conferring raltegravir resistance.

- Signature integrase mutations Q148H/K/R and N155H, as individual mutations, confer reduced susceptibility and viral replication capacity.
  - More than 1 mutation is needed to engender high level of resistance.
  - No association between dose and/or drug concentration and resistance.

- Analysis of longitudinal resistance data is ongoing.
Raltegravir Resistance and Clinical Implication

- In patients failing a raltegravir-containing regimen, the HIV isolate often displayed integrase mutations conferring raltegravir resistance.

- Signature integrase mutations Q148H/K/R and N155H, as individual mutations, confer reduced susceptibility and viral replication capacity.
  - More than 1 mutation is needed to engender high level of resistance.
  - No association between dose and/or drug concentration and resistance.

- Analysis of longitudinal resistance data is ongoing.

- Factors that decrease the development of resistance:
  - Lower viral load
  - First use of enfuvirtide/darunavir in OBT
  - PSS > 0
  - GSS > 0

- Raltegravir should be used in combination with other potent active agents to maximize its clinical benefits.
Agenda

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  - Clinical Trials Results
    - Efficacy
    - Resistance
    - Safety

- Robin Isaacs, MD
  - Drug-Drug Interactions
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  - Conclusions
Number of Patients Exposed to Raltegravir ≥400 mg BID Phase II and III Studies

- Entire study period
  - Includes double-blind plus all open-label therapy phases
    - At least 16 weeks: 650 patients
    - At least 24 weeks: 430 patients
    - At least 48 weeks: 134 patients
Phase II and III Safety Database

Patients treated with raltegravir
All doses (100, 200, 400, and 600 mg) – Double-Blind, Open-Label Post-virologic Failure, and Open-Label Extension
N=878 patients
Phase II and III Safety Database

Patients treated with raltegravir
All doses (100, 200, 400, and 600 mg) – Double-Blind, Open-Label Post-virologic Failure, and Open-Label Extension
N=878 patients

**Double-Blind Phase**

Raltegravir 400 mg
Treatment-experienced patients
P005, P018, P019
507 patients on raltegravir
[261 patient-years of exposure]
282 patients on placebo
[127 patient-years of exposure]
Phase II and III Safety Database

Patients treated with raltegravir
All doses (100, 200, 400, and 600 mg) – Double-Blind, Open-Label Post-virologic Failure, and Open-Label Extension
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- Treatment-experienced patients
  - P005, P018, P019
  - 507 patients on raltegravir
  - [261 patient-years of exposure]
  - 282 patients on placebo
  - [127 patient-years of exposure]

### Raltegravir all doses

- All patients
  - P004, P005, P018, P019
  - N=758 patients on raltegravir
  - versus 323 on control
Phase II and III Safety Database

Patients treated with raltegravir
All doses (100, 200, 400, and 600 mg) – Double-Blind, Open-Label Post-virologic Failure, and Open-Label Extension
N=878 patients

<table>
<thead>
<tr>
<th>Double-Blind Phase</th>
<th>Open-Label Post-virologic Failure</th>
<th>Open-Label Extension†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Raltegravir 400 mg</td>
<td>Raltegravir 400 mg</td>
<td>Raltegravir 400 mg</td>
</tr>
<tr>
<td>Treatment-experienced patients</td>
<td>Treatment-experienced patients</td>
<td>Treatment-experienced patients</td>
</tr>
<tr>
<td>P005, P018, P019</td>
<td>P005, P018, P019</td>
<td>P005</td>
</tr>
<tr>
<td>507 patients on raltegravir</td>
<td>282 patients on placebo</td>
<td>N=6 patients†</td>
</tr>
<tr>
<td>[261 patient-years of exposure]</td>
<td>[127 patient-years of exposure]</td>
<td></td>
</tr>
<tr>
<td>Raltegravir all doses</td>
<td>Raltegravir 400 mg</td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td>Treatment-experienced patients</td>
<td></td>
</tr>
<tr>
<td>P004, P005, P018, P019</td>
<td>P005</td>
<td></td>
</tr>
<tr>
<td>N=758 patients on raltegravir</td>
<td>N=114 patients†</td>
<td>N=6 patients†</td>
</tr>
<tr>
<td>versus 323 on control</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

† Includes only patients who came from placebo group.
‡ After ≥24 weeks of double-blind treatment, all patients switched to raltegravir 400 mg in an open-label extension.
Phase I and Phase II

- Generally well tolerated in healthy subjects
- In dose-ranging studies in treatment-naïve and treatment-experienced patients
  - Generally well tolerated
    - Clinical and laboratory adverse experience profile similar to control groups
    - No dose-limiting toxicities
    - No dose-related toxicities
- In treatment-naïve patients, in combination with lamivudine and tenofovir
  - No impact on serum cholesterol, LDL-cholesterol, and triglycerides at Week 48
Integrated Summary of Safety

Raltegravir 400 mg BID

Protocol 005, Protocol 018, and Protocol 019

Double-Blind Phase
### Clinical Adverse Experiences
#### Double-Blind Phase

<table>
<thead>
<tr>
<th>Adverse Experience</th>
<th>Raltegravir(\dagger) N=507 %</th>
<th>Placebo(\dagger) N=282 %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any adverse experience</td>
<td>81.1</td>
<td>84.4</td>
</tr>
<tr>
<td>Drug-related(\ddagger) adverse experience</td>
<td>47.7</td>
<td>51.8</td>
</tr>
<tr>
<td>Serious adverse experience</td>
<td>10.7</td>
<td>12.8</td>
</tr>
<tr>
<td>Serious drug-related(\ddagger) adverse experience</td>
<td>1.6</td>
<td>1.8</td>
</tr>
<tr>
<td>Death</td>
<td>1.2</td>
<td>1.1</td>
</tr>
<tr>
<td>Adverse experience leading to discontinuation</td>
<td>1.6</td>
<td>2.1</td>
</tr>
</tbody>
</table>

\(\dagger\) Plus OBT.

\(\ddagger\) Determined by the investigator to be possibly, probably, or definitely related to any drug in the regimen (raltegravir/placebo alone or in combination with OBT, or OBT alone).
Drug-Related† Clinical Adverse Events
Any Intensity – Double-Blind Phase Incidence ≥2% in Any Treatment Group

<table>
<thead>
<tr>
<th></th>
<th>Raltegravir† (% N=507)</th>
<th>Placebo† (% N=282)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal distension</td>
<td>2.0</td>
<td>2.1</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>2.8</td>
<td>2.1</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>8.7</td>
<td>11.0</td>
</tr>
<tr>
<td>Flatulence</td>
<td>2.2</td>
<td>1.8</td>
</tr>
<tr>
<td>Nausea</td>
<td>6.3</td>
<td>8.2</td>
</tr>
<tr>
<td>Vomiting</td>
<td>2.6</td>
<td>4.6</td>
</tr>
<tr>
<td>Fatigue</td>
<td>2.8</td>
<td>1.4</td>
</tr>
<tr>
<td>Injection site reaction</td>
<td>8.7</td>
<td>9.6</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>1.0</td>
<td>2.1</td>
</tr>
<tr>
<td>Headache</td>
<td>4.7</td>
<td>5.7</td>
</tr>
</tbody>
</table>

† Determined by the investigator to be possibly, probably, or definitely related to any drug in the regimen (raltegravir/placebo alone or in combination with OBT, or OBT alone).
‡ Plus OBT.
### Drug-Related† Clinical Adverse Events
**Moderate/Severe Intensity - Double-Blind Phase**
**Incidence ≥2% in Any Treatment Group**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Raltegravir ‡</th>
<th>Placebo ‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>3.7%</td>
<td>3.5%</td>
</tr>
<tr>
<td>Nausea</td>
<td>2.2%</td>
<td>3.2%</td>
</tr>
<tr>
<td>Headache</td>
<td>2.2%</td>
<td>1.4%</td>
</tr>
<tr>
<td>Injection site reaction</td>
<td>2.4%</td>
<td>2.8%</td>
</tr>
</tbody>
</table>

† Determined by the investigator to be possibly, probably, or definitely related to any drug in the regimen (raltegravir/placebo alone or in combination with OBT, or OBT alone).
‡ Plus OBT.
Drug-Related† Laboratory Adverse Events
Double-Blind Phase
Incidence ≥2% in Any Treatment Group

<table>
<thead>
<tr>
<th></th>
<th>Raltegravir†</th>
<th>Placebo†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=507</td>
<td>N=282</td>
</tr>
<tr>
<td>n/m</td>
<td>%</td>
<td>n/m</td>
</tr>
<tr>
<td>↑ Serum ALT</td>
<td>16/507</td>
<td>2/282</td>
</tr>
<tr>
<td>↑ Serum AST</td>
<td>13/507</td>
<td>3/282</td>
</tr>
<tr>
<td>↑ Serum creatinine</td>
<td>7/507</td>
<td>6/282</td>
</tr>
<tr>
<td>↑ Serum triglycerides</td>
<td>13/507</td>
<td>3/279</td>
</tr>
</tbody>
</table>

† Determined by the investigator to be possibly, probably, or definitely related to any drug in the regimen (raltegravir/placebo alone or in combination with OBT, or OBT alone).
‡ Plus OBT.
n/m = number of patients with laboratory adverse experiences / number of patients for whom the laboratory test was recorded postbaseline.
## Selected Laboratory Abnormalities

### Double-Blind Phase

<table>
<thead>
<tr>
<th>Test</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total serum bilirubin</strong></td>
<td>1.6 - 2.5 x ULN</td>
<td>2.6 - 5.0 x ULN</td>
<td>&gt;5.0 x ULN</td>
</tr>
<tr>
<td><strong>Serum AST</strong></td>
<td>2.6 - 5.0 x ULN</td>
<td>5.1 - 10.0 x ULN</td>
<td>&gt;10.0 x ULN</td>
</tr>
<tr>
<td><strong>Serum ALT</strong></td>
<td>2.6 - 5.0 x ULN</td>
<td>5.1 - 10.0 x ULN</td>
<td>&gt;10.0 x ULN</td>
</tr>
<tr>
<td><strong>Serum alkaline phosphatase</strong></td>
<td>2.6 - 5.0 x ULN</td>
<td>5.1 - 10.0 x ULN</td>
<td>&gt;10.0 x ULN</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Raltegravir† N=507</th>
<th>Placebo† N=282</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>%</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total serum bilirubin</td>
<td>5.5</td>
<td>6.4</td>
</tr>
<tr>
<td>Serum AST</td>
<td>8.9</td>
<td>4.6</td>
</tr>
<tr>
<td>Serum ALT</td>
<td>6.7</td>
<td>7.8</td>
</tr>
<tr>
<td>Serum alkaline phosphatase</td>
<td>1.8</td>
<td>0.4</td>
</tr>
</tbody>
</table>

† Plus OBT; ULN = upper limit of normal.
Evaluation of Liver Function Test Results by Hy’s Law - Double-Blind Phase

- Key elements of Hy’s Law
  - Laboratory criteria
    - AST and/or ALT ≥3x ULN
    - Total bilirubin ≥2x ULN
    - No marked increase in alkaline phosphatase (≤5x ULN)
  - Absence of clinical confounders

No Patients Met Criteria for Hy’s Law

- Patients meeting laboratory criteria but had clinical confounders
  - Raltegravir (n=4)
    - Stable Grade 3 ↑ bilirubin due to atazanavir with transient AST/ALT elevation
    - Documented HBV reactivation due to stopping medications
    - Chronic HCV infection with transient flare
    - Complicated patient with multiple confounding factors
      - Concurrent acute thyrotoxicosis and acute respiratory syndrome
      - Fatal bronchopneumonia with septic shock
  - Placebo (n=0)
Safety in Special Groups

- **Intrinsic factors**
  - Similar safety profile
    - Age (adults ≤65 years)
    - Race
    - Gender

- **Extrinsic factors**
  - Generally well tolerated with similar safety profile when used in combination with atazanavir and/or tenofovir
  - Hepatitis B and/or C virus infection
    - Safety profile in patients with hepatitis B and/or hepatitis C co-infection was similar to that in patients without co-infection
    - Rates of AST and ALT abnormalities were somewhat higher in the subgroup with hepatitis B and/or hepatitis C co-infection for both the raltegravir and placebo groups
Rare Serious Adverse Experience Malignancies

- Imbalance in number of malignancies in raltegravir group in original application
  - Comprehensive review undertaken in original application
    - Primary population: All patients receiving raltegravir in double-blind period of Phase II and Phase III studies
      - Raltegravir group: N=758; 508 PY
      - Comparator group: N=323; 169 PY

- Updated review through 09 July 2007†
  - Same studies/patient population; same analysis method
  - ~60% greater exposure than original application
    - Raltegravir group: N=758; 820 PY
    - Comparator group: N=323; 261 PY
  - Imbalance in number of malignancies has not been sustained with additional follow-up

PY = patient-years of exposure.
† Data submitted and under review by FDA.
# Summary of Malignancy – Double-Blind Phase

## Phase II and III Studies

### Original Application

<table>
<thead>
<tr>
<th>Patients with malignancy</th>
<th>Raltegravir N=758; 508 PY</th>
<th>Comparator Group N=323; 169 PY</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)†</td>
<td>Recurrent</td>
</tr>
<tr>
<td>Kaposi’s sarcoma</td>
<td>2 (0.3)</td>
<td>1</td>
</tr>
<tr>
<td>Non-Hodgkin’s lymphoma</td>
<td>3 (0.4)</td>
<td>1</td>
</tr>
<tr>
<td>SC carcinoma – anogenital</td>
<td>1 (0.1)</td>
<td>-</td>
</tr>
<tr>
<td>SC carcinoma – other</td>
<td>1 (0.1)</td>
<td>-</td>
</tr>
<tr>
<td>Rectal cancer</td>
<td>1 (0.1)</td>
<td>-</td>
</tr>
<tr>
<td>Hepatocellular carcinoma</td>
<td>1 (0.1)</td>
<td>-</td>
</tr>
<tr>
<td>Non-melanoma skin cancer</td>
<td>1 (0.1)</td>
<td>1</td>
</tr>
</tbody>
</table>

PY = patient-years of exposure, SC = squamous cell.

† Crude incidence (100×n/N).

‡ Diagnosis of cancer occurred within 3 months of initiating study therapy.

Patients with multiple events may be counted more than once in different terms, but only once in one term.
## Summary of Malignancy – Double-Blind Phase Phase II and III Studies  
Cumulative Update as of 09 July 2007*

* Data submitted and under review by FDA.  
PY = patient-years of exposure, SC = squamous cell.  
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‡ Diagnosis of cancer occurred within 3 months of initiating study therapy.  
Patients with multiple events may be counted more than once in different terms, but only once in one term.

### Patients with malignancy

<table>
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<th>Comparator Group N=323; 261 PY</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)‡</td>
<td>Recurrent</td>
</tr>
<tr>
<td>Kaposi’s sarcoma</td>
<td>4 (0.5)</td>
<td>3</td>
</tr>
<tr>
<td>Non-Hodgkin’s lymphoma</td>
<td>3 (0.4)</td>
<td>1</td>
</tr>
<tr>
<td>SC carcinoma – anogenital</td>
<td>5 (0.7)</td>
<td>2</td>
</tr>
<tr>
<td>SC carcinoma – other</td>
<td>1 (0.1)</td>
<td>-</td>
</tr>
<tr>
<td>Rectal cancer</td>
<td>1 (0.1)</td>
<td>-</td>
</tr>
<tr>
<td>Hepatocellular carcinoma</td>
<td>1 (0.1)</td>
<td>-</td>
</tr>
<tr>
<td>Non-melanoma skin cancer</td>
<td>5 (0.7)</td>
<td>2</td>
</tr>
<tr>
<td>Metastatic neoplasm</td>
<td>0 (0)</td>
<td>-</td>
</tr>
</tbody>
</table>
# Summary of Malignancy Rates and Relative Risk

Double-Blind Phase

<table>
<thead>
<tr>
<th>Timing</th>
<th>Raltegravir (N=758 Patients)</th>
<th>Comparator Group (N=323 Patients)</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Original Application</td>
<td>10</td>
<td>1</td>
<td>3.3 (0.5, 144)</td>
</tr>
<tr>
<td>09Jul07†</td>
<td>19</td>
<td>5</td>
<td>1.2 (0.4, 4.1)</td>
</tr>
</tbody>
</table>

PY = patient-years of exposure.
† Per 100 PY.
† Data submitted and under review by FDA.
Summary of Malignancies

- In original application, imbalance in number of malignancies was noted in raltegravir group
  - No specific cancer risk attributable to raltegravir is apparent
    - Malignancy types are those anticipated in an AIDS population
    - Malignancy rates in the raltegravir group are consistent with those seen in a severely immunodeficient AIDS population
    - Many of the malignancies in the raltegravir group likely present at time of study entry or recurrences of prior diagnosed malignancies

- Based on the most up-to-date analysis†, this imbalance in number of malignancies has not been sustained with additional follow-up

- Further follow-up is proposed in the Risk Management Plan

† Data submitted and under review by FDA.
In patients with advanced HIV-1 infection, failing antiretroviral therapies with multi-drug-resistant virus, raltegravir in combination with OBT

- Was generally well tolerated with no dose-limiting toxicities
- Safety profile comparable to that of placebo with OBT
  - Raltegravir was well tolerated in patients regardless of race, age, and gender and in patients with hepatitis B and/or C co-infection
- Few adverse experiences leading to discontinuations